CLINICAL REVIEW DOCUMENT

Biological License Application 97- 1325
Receipt Date 12/05/97

USAN Name: **DAB_{389}IL-2; denileukin diftitox for injection**
Trade Name: **Ontak™ (Seragen)**
Sponsor: Seragen, Ind.

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I. PROPOSED INDICATION

"Ontak is indicated for the treatment of patients with cutaneous T-cell lymphoma (CTCL) which is persistent or recurrent despite prior therapy."

II. REGULATORY HISTORY

This is the original application for denileukin diftitox. This product is also being evaluated in clinical trials for the treatment of [redacted]. Denileukin diftitox has been granted orphan drug designation for the treatment of CTCL.

The products, which are currently approved for the treatment of CTCL, include cyclophosphamide, methotrexate, vinblastine, corticosteroids, oxsoralen in conjunction with the UVAR photopheresis system. Cyclophosphamide, methotrexate, and vinblastine are indicated for the treatment of advanced stages of CTCL only. The UVAR® system (used in conjunction with oxsoralen) was approved in 1987 and is indicated for the palliative treatment of the skin manifestations of CTCL in persons who have not been responsive to other forms of treatment.

III. OVERVIEW OF CTCL

A. Background and staging

CTCL is a malignant cutaneous lymphoproliferative disorder of CD4 (helper T, T_4-cells) cells, with an incidence of 1000 new cases/yr. This subtype of non-Hodgkin's lymphoma exhibits epidermotropism, which is postulated to be due to the ICAM-1 on keratinocytes binding to the LFA-1 on the malignant lymphocytes.

CTCL, commonly referred to as mycosis fungoides MF, is a disease in which localized plaques evolve into tumor nodules. When the disease progresses to a stage at which circulating lymphomatous T_H-cells are detected, the term Sézary Syndrome (diffuse exfoliative erythroderma with greater than 10% abnormal circulating cells) is used. The malignant lymphocytes are cerebriform and hyperchromatic with convoluted nuclei; in skin biopsies the histopathology demonstrates atypical T cells with irregular cerebriform nuclei (MF cells) infiltrating the epidermis and the zone beneath this. When the zone beneath the epidermis is infiltrated, the areas with collections of abnormal T-cells are called Pautrier's microabscesses.

The prognosis for CTCL is correlated with the stage of disease at presentation. The staging system commonly used in clinical studies (but not in the studies conducted by Seragen) is a modification of the TNM classification developed by the Mycosis Fungoides Cooperative Group and published by Bunn and Lamberg (below). The overall median survival is 8 to 9 years from time of diagnosis.

T: Skin Involvement

TO: Lesions clinically an&or histopathologically suggestive of CTCL

T 1: Limited plaques, papules, or eczematous patches covering < 10% of skin surface

T2: Generalized plaques, papules, or erythematous patches covering ≥ 10% of skin surface

T3 : Cutaneous tumors

T4: Generalized erythroderma

N: Lymph Nodal Involvement

NO: No palpable lympadenopathy; no lymph node pathology

N 1: Palpable lympadenopathy; no lymph node pathology

N2: No palpable lympadenopathy; positive lymph node pathology

N3 : Palpable lympadenopathy; positive lymph node pathology

B: Blood Involvement

BO: < 5% atypical circulating cells

B 1: ≥ 5% atypical circulating cells

M: Visceral Involvement

MO: No visceral organ involvement

Ml : Visceral organ involvement; positive pathology

TABLE 1: STAGING SYSTEM FOR CTCL

STAGE	CHARACTERISTICS	TNM STAGE	SURVIVAL
I a	Limited plaques (T1; < 10% BSA); no adenopathy	T1 N0 M0	> **12** years
I b	Generalized plaques (T2); no adenopathy	T2 NO MO	> 12 years
II a	Plaques with adenopathy [negative histology (N 1)]	Tl-2Nl MO	**2** to 4 years
II b	Cutaneous tumors (T3) ± adenooathv (NO- 1)	T3 NO-1 MO	2 to 4 years
III	Generalized erythroderma (T4) ± adenopathy (NO- 1)	T4 NO-l MO	**2** to 4 years
IV a	Histologically involved nodes ± adenopathy	Tl-4 N2-3 MO	< **2.5** years
IV b	Visceral metastasis (M 1), any cutaneous or nodal stage	T1-4 NO-3 M1	< **2.5** years

There is no curative treatment for CTCL. Therapeutic approaches for CTCL include topical agents (glucocorticoids, nitrogen mustard). radiotherapy. PUVA with methoxypsoralen (methoxasalen), and systemic treatment with single agent or combination chemotherapy (CHOP).

B. Treatment of Early stage disease (Stages Ia and Ib)

Use of topical agents is utilized for treatment of early stage disease and/or for symptom palliation. Topical glucocorticoids are useful for minimal lesions that are histopathologically suggestive of CTCL (Stage 0). Topical nitrogen mustard is considered first line therapy for early stage plaque disease, with reported response rates ranging from 30-60%, with up to 20% durable complete responses. Responses are observed more commonly in patients with limited numbers of plaque (Ia) as compared to those with generalized plaque involvement (Ib). Responses may be observed after several months of therapy in conjunction with maintenance topical therapy administered for one to two years. Toxicities of treatment include hypersensitivity reactions and secondary skin cancers.

Another therapeutic approach consists of psoralens utilized in conjunction with ultraviolet light (PUVA). Psoralen intercalate with DNA; on exposure to UV light, DNA adducts are formed. Because UV-A (spectrum is 320 - 400 nm) does not penetrate beyond the epidermis and upper dermis, this therapy is utilized primarily for treatment of plaque disease. PUVA is a commonly used first line treatment for Stages I-IIa disease, and for secondary treatment after topical steroids for Stage 0 disease. Response rates vary with the extent of cutaneous disease; it is reported to be as high as a 90% complete response rate in patients with minimal skin disease (Ia) while the response rate is 70% in patients with infiltrative plaques. Following response, maintenance treatment at weekly to monthly intervals is employed. Relapse following cessation of PUVA can be successfully managed with reinstitution of PUVA therapy. Acute complications of this treatment include erythema, pruritus, skin dryness, and nausea. Cataracts and secondary skin cancers have been reported as chronic or delayed toxicities,

Cis-retinoic acid has been reported to result in a 40% response rate in patients with stages Ia and Ib disease, however, responses have not been prolonged (last less than 1 year).

C. Treatment of advanced stage disease (Stages IIa-IV)

There are no curative therapies for advanced stage disease, however responses are observed in such patients. Electron beam radiotherapy is an effective initial treatment for patients with stage IIb disease resulting in durable remissions. However, this technique is technically demanding and limited in availability to specific treatment centers. Acute toxicities include erythema, temporary epilation, temporary loss of nails, and impaired perspiration. Chronic toxicities include dry skin, telangiectasia. and secondary skin cancers.

Extracorporeal photochemotherapy. termed as photopheresis with methoxsalen. serves as first-line therapy for Stage III (erythrodermic disease) and is indicated for palliative treatment of skin manifestations of CTCL in patients with refractory disease. Methoxsalen forms mono- and bi-functional adducts on DNA and works as a photosensitizer. Subsequent to administration of the oral methoxsalen, the patient undergoes photopheresis. Photopheresis involves the use of UV-A radiation upon leukocytes obtained by leukapheresis; these leukocytes are then re-infused into the patient. The resultant alteration of the leukocytes' cell-surface antigens is thought to stimulate a host response. Clinical studies have demonstrated >50% clinical complete response rates, with improvement in quality of life. The most common side effect is transient nausea from the use of methoxsalen.

Single agents which have been reported to show clinical activity in Stage IV disease and refractory disease include methotrexate. cyclophosphamide. chlorambucil. etoposide. and cisplatin. Combination chemotherapy regimens. which have been utilized. include CVP. chlorambucil/prednisone, CHOP, and a variety of other regimens commonly used for treatment of B-cell NHL. In general. the response rates for combination chemotherapy is higher than for single agent chemotherapy.

Interferon alfa has been evaluated in both heavily pretreated and minimally pre-treated patients. In minimally pretreated patients, response rates of up to 90% have been reported, while response rates in more heavily treated or refractory patients is closer to 50%. Reported toxicities include constitutional symptoms (fever, chills, myalgias) and moderate to severe neurological toxicities. Combined modality therapies, such as combinations of radiotherapy and chemotherapy, appear to provide higher response rates in patients with advanced disease (over combination chemotherapy alone) but are associated with greater toxicity.

IV. Clinical Studies

A. Clinical Information submitted to BLA Reference Number 97-1325

12/5/97: Original Submission

- Final study report for Protocol 92-04-01
- Final study report for Protocol 93-04-10
- Interim study report for Protocol 93-04-11
- Interim study report for Protocol 93-04-14
- Summary information for 7 studies conducted with DAB IL-2 in lymphoma

3/30/98: Response to information requests

7/14/98: ODAC briefing document

8/06/98: Response to complete review letter

10/98 to 12/11/99: Multiple submissions regarding Immunohistochemistry assay

B. Product characterization

Denileukin diftitox is a 58 kD fusion protein consisting of interleukin-2 and a truncated portion of the diphtheria toxin molecule (389 amino acids encoding for the A and B chain sequences. but not the terminal binding portion). The product is expressed in *E. coli*. An earlier version of the product was studied in Phase 1 and 2 trials, which contained a — amino acid sequence for the diphtheria toxin.

The proposed mode of action is through binding of the IL-2 portion of the molecule to the IL-2 receptor on the malignant cells. Once bound to the cell surface, the protein is internalized. The diphtheria toxin portion of the molecule inhibits : ——————————— which results in inhibition of protein synthesis and leads to cell death. While the primary target of the fusion protein is the malignant cell, treatment is likely to result in the killing of non-malignant, activated IL-2-receptor positive T-cells. Of note. the IL-2 receptor is also present on activated T-cells, B-cells, macrophages. and oligodendroglial cells. A potential consequence of such cross-reactive targeting of normal tissues is impairment of normal immunologic function.

C. Individual Clinical Studies

(1) Clinical studies conducted with DAB IL-2

Supportive information was derived from seven Phase I/II studies conducted with DAB IL-2, an earlier investigational construct of the immunotoxin. The design, eligibility criteria, treatment plan and number of patients enrolled in the 7 studies are summarized in Table 2.

This product, DAB, IL-2, differed from the one for which licensure is being sought (DAB_{389}IL-2) in the length of the Diphtheria toxin component of the fusion protein. The DAB IL-2 product contained a longer sequence, — amino acids as compared to 389 amino acids, encoding the Diphtheria toxin.

Summary results: There were 36 patients with CTCL who were enrolled in 7 studies of DAB IL-2. The response rate was 17% (6 of 36). Response durations were 1, 2, 4, 8, >18, and >72 months. The patient with a prolonged response to treatment had stage Ia CTCL.

Toxicities observed in these trials included transaminitis, hypoalbuminemia, hypersensitivity reactions, rash, thrombocytopenia, and renal dysfunction with elevated serum creatinine.

Immunogenicity: At entry, the presence of anti-Diphtheria toxin antibodies was detected in 30% of the patients. Following treatment with DAE, IL-2, 60 % of patients had anti-Diphtheria toxin antibodies.

TABLE 2: DAB IL2 Cancer Studies

Protocol	Design	Population	#Pts	#Pts w/ CTCL	Dose Range (µg/kg/day)	Schedule*
88-001	Open label, dose-escalation	IL-2R⊕ hematologic cancers	18	1	0.7 – 200	IV bolus on days 1 & 3 then daily x 7
39-01-02	Open label. dose-escalation	IL-2R⊕ hematologic cancers	17	5	12.5 – 100	IV bolus daily x 5 (10 pts) or 3-hr IV infusions weekly(7pts)
89-O l-04	Open label. dose-escalation	IL-2R⊕ hematologic cancer	15	0	75 – 200	30-minute IV infusions, daily x 5
90-O l-07	Open label. dose-escalation	CLL, B-cell NHL, CTCL, ATL, HD; & IL-2R⊕ cancers	23	3	150 -400	90-minute IV infusions, daily x 5
90-O l-08	Open label, dose-escalation	Malignant lymphoproliferative disorders	17	3	100-300	6-hour IV infusions days 1, 2, 8, 9, 15& 16
90-O l-09	Open label, dose-escalation	CLL, B-cell NHL, CTCL, ATL, HD; other IL-2R⊕	20	10	90 – 270	30-min IV infusions BID daily x 4 days

91-01-l 1	Open label, single arm	CTCL	14	14	200	90-minute IV infusions daily x 5

Subsequent courses were given q 3-4 wks if patients tolerated therapy (I Grade III toxicity).

(2) Protocol 92-04-o 1

Protocol Synopsis

Title: Phase I/II Dose-Escalation Study of $DAB_{389}IL\text{-}2$ in Low- and Intermediate-Grade Non-Hodgkin's Lymphoma, Hodgkin's Disease and Cutaneous T-Cell Lymphoma Patients Who Have Relapsed Following Standard Therapy

Study Design: Multicenter, open-label, dose-escalation with ≥ 3 patients/dose cohort

Objectives.

- To evaluate the safety (obtaining the MTD and DLT), tolerability, and immunogenicity of citrate-formulated DAB389IL-2 given intravenously (IV) daily x 5.
- To characterize the pharmacokinetics of the therapy following a single IV bolus in these patients.
- To demonstrate preliminary evidence of anti-tumor effects.
- To assess changes in symptoms and functional status in association with therapy.

End-points (secondary end-points are not analyzed in this report).

- Primary – the MTD (the dose at which 2/6 patients naïve to DAB389IL-2 at a dose-level) experience a drug-related DLT during the 1st course of therapy. If, at any dose level, 2 naive patients experience a DLT. 3 additional naive patients should be studied. If DLT occurs in 1 more patient, then that dose will be judged to be above the MTD, with the MTD being the next lower dose-level.
- Secondary – standard pharmacokinetic data (serum concentrations; steady state levels; $t_{1/2}$); adverse events, demographics and anti-tumor effects.

Inclusion Criteria: Patients with IL-2 receptor-positive NHL (all grades, based upon the International Working Formulation), HD (all stages, based upon the Modified Ann Arbor Staging System), and CTCL (Stage I - IV by a modification of TNM Classification by Bunn and Lamberg), failing standard therapies, good organ function, Karnofsky performance status ≥ 70%; ≥ 3 months life-expectancy.

Exclusion Criteria: Active infection, HIV antibody seropositive; hepatitis B surface antigen positive; pregnancy.

Treatment Plan:

Sequential cohorts of patients were enrolled into the following dose level cohorts:

- [redacted] formulation: 150, 300,450, 600, 750, 900, 1050 kU/kg/day (1 O/19/92-7/9/94)

- *Citrate* formulation: 25, 30, 35, and 40 µg/kg/d BCA' (7/10/94-3/3/95)
- DAP_ 'L-2 was administered as an IV bolus over 5- 15 minutes daily for 5 days. Repeat cycles were to be administered every 18 to 21 days for a maximum of 6 cycles.
- Acceptable concomitant medications: acetaminophen, antihistamines, antibiotics, and analgesics. Corticosteroids in a dose equivalent or higher than 20 mg prednisone po daily was prohibited

Tumor response criteria.

- Complete response (CR): No evidence of active disease for ≥ 4 weeks with no new evidence of disease
- Partial response (PR): A reduction in measurable disease of 250% for ≥4 weeks, with no new lesions.
- Stable disease (SD): ≤25% increase or <50% decrease in measurable disease, no new lesions
- Progressive disease (PD): >25% increase in disease or new lesions

Monitor/Assessment	DAY							
	Screen	1	3	5	8-9	10-12	16-18	18-21
Physical exam	X			X				X-d 21
CBC with differential and platelet count	X	X		X	X		X	
Chemistries (hepatic and renal function)	X	X		X	X	X	X	
Urinalysis	X	X		X	X		X	
FACS analysis of lymphocyte subsets	X	X	X		X			
Antibodies to DAB_{389}IL-2, diphtheria toxin and IL-2	X							X

Analytic Plan: Descriptive statistics for adverse events.

Amendments

1. Version 3.1 (effective 10 Mar 1993) Permitted enrollment up to 9 patients with NHL with high-grade disease
2. Version 3.2 (effective 14 Apr 1993) Added inclusion criteria for IL-2R-expression on HD tumors
3. Version 3.3 (effective14 May 1993) Added additional dose levels to continue to MTD: 900, 1050, 1200, and 1350 kU/kg/d. Change duration of infusion from 5 to 15 minutes.
4. Version 3.4 (effective1 0 Jul 1994) Change DAB389IL-2 formulation from ——— to citrate; indicate new dose units for the 900, 1050, 1200, and 1350 dose levels into (respectively) 25, 30, 35, and 40 µg/kg/d BCA.

(i) ———————————

1 **Dose for citrate formulation based on protein mass as determined by BCA** colorimetric **method**

Results:

Patient enrollment and disposition

The study was conducted at 9 institutions. A total of 230 patients were screened for enrollment. One hundred twenty-one patients (53%) were excluded for lack of IL-2 receptor or insufficient information to determine the IL-2 receptor status on the tumor. An additional 36 patients failed to meet other eligibility criteria at screening.

There were 73 patients who were enrolled and treated between October 19, 1992 and March 3, 1995. The first 50 patients enrolled in the study received only the [redacted] ouffered formulation; three subsequent patients initiated treatment with the [redacted] ouffered formulation and were switched to the citrate formulation during the course of the study. The last 20 patients received only the citrate formulation. There were 6 patients enrolled in the study who had received DAP_ IL-2 in other studies.

The 73 patients consisted of 35 (49%) patients with CTCL, 17 (23%) patients with NHL and 21 (29%) patients with Hodgkin's disease. Twenty patients (27%) completed the planned course of 6 cycles. The majority, 37 of the 73 patients (5 1%), discontinued treatment for progressive disease. Twelve patients (16%) discontinued treatment for adverse events, 3 (4%) withdrew consent (one to seek alternative therapy), and 1 (1%) patient died on study.

Among the 35 patients with CTCL, 12 (34%) completed all planned therapy, 13 (37%) withdrew due to progressive disease, 8 (23%) withdrew for adverse events and 2 withdrew consent (one of these to seek other therapy). Four patients with HD and four with NHL completed the treatment course, 19% and 24%, respectively. Fourteen (67%) and 10 (59%) of HD and NHL patients, respectively, discontinued treatment for disease progression and two patients each with HD and NHL discontinued treatment due to adverse events. The median number of cycles received was 3 for patients with CTCL and 2 for patients with HD or NHL.

TABLE 3: Patient Disposition in Protocol 92-04-01

Study Status	Non-CTCL	CTCL	Combined
	N = 38	N = 35	N = 73
Completed 6 cycles			
Yes	8 (21 %)	12 (34 %)	20 (27 %)
Reason for Study Discontinuation (% of total enrolled)			
Disease Progression	24 (63 %)	13 (37 %)	37 (51 %)
Adverse Event(s)	4 (10 %)	8 (23 %)	12 (16 %)
Withdrew consent	1 (3 %)	2 (6 %)	3 (4%)
Death	1 (3 %)	0 (0 %)	1 (1 %)

Protocol deviations

The protocol was amended four times (see above). Seragen allowed 6 patients with stable or

responding disease to receive two additional cycles of therapy and granted 10 requests for protocol deviations: 8 were waivers of protocol eligibility criteria. Two patients were allowed to "re-enter" the study. One patient who had withdrawn from therapy for an adverse event in cycle 1, received no additional treatment, and was allowed to "continue" therapy 9 months later. A second patient left the study after 5 cycles to receive chemotherapy; this subject was allowed to "continue" therapy after failing to respond to chemotherapy. Two patients were enrolled without assessment of tumor histology. One patient received was overdosed throughout the treatment period. This subject was assigned to the 150 kU/kg/d level and received dose based on weight in lbs rather than kg (approximately 300 kU/kg/d).

Patient population

The baseline entry characteristics for the study population are presented in Table 4. The study population was heavily pretreated, with a median of 4 prior therapeutic interventions among patients with Hodgkin's disease (range 3-10) and NHL (range 2-l 0) and a median of 3 prior therapeutic interventions among patients with CTCL (range 0- 15). All Hodgkin's and NHL patients had received prior chemotherapy and 66% of the CTCL patients had received prior chemotherapy. Among patients with Hodgkin's disease, 90% had undergone high-dose chemotherapy with stem cell support, 7 1% had received radiotherapy and 19% had received biological response modifiers (including 2 patients who had received DAB,IL-2). Among patients with NHL, 29% had undergone high-dose chemotherapy with stem cell support, 35% had received radiotherapy and-l 8% had received biological response modifiers. Among the 35 patients with CTCL, 71% had received phototherapy and 37% had received topical therapy. 1(3%) had undergone high-dose chemotherapy with stem cell support, 29% had received radiotherapy and 46% had received biological response modifiers (predominantly interferon alfa). Four patients with CTCL had received DAF,IL-2 and one patient with stage Ib disease had received no prior therapy. Baseline characteristics for important prognostic factors are presented in Table 4.

Table 5 provides a summary of patient characteristics according to dose cohort. All dosing information is reported in citrate equivalent doses'. Patients with CTCL were enrolled in all dose levels while fewer patients with HD or NHL were enrolled in the higher dose level cohorts. For patients with CTCL there were fewer patients with advanced stages of disease (III - IV b) enrolled at doses > 19 µg/kg/d (citrate equivalent).

(i) ———————

2 Citrate equivalent doses, based upon mass as measured by ——— rather than the BCA method, are provided for all patients. Citrate equivalent doses in µg/kg/d ——— are provided in parentheses for each of the dose level cohorts: 150 kU/kg/d (3); 300 kU/kg/d (6); 450 kU/kg/d (9); 600 kU/kg/d (12); 750 kU/kg/d (15); 900 kU/kg/d (19); 25 µg/kg/d BCA (19); 1050 kU/kg/d (2 1); 30 µg/kg/d BCA (23); 35 µg/kg/d BCA (27); 40 µg/kg/d BCA (3 1)

TABLE 5: Patient Entry Characteristics By Dose-Level

Variable	Citrate Equivalent Dose (µg/kg)[3]					All Pts
	3 - 9	12 - 15	19	23 - 27	31	
Age						
Mean ± SD	48 ± 20	51 ± 17	48 ± 18	56 ± 18	58 ± 21	51 ± 18
Range	16 - 77	20 - 78	23 - 81	24 - 79	32 - 77	16 - 81
Gender						
Male	10 (53 %)	10 (56 %)	11 (61 %)	8 (62 %)	5 (100 %)	44 (60 %)
Female	9 (47 %)	8 (44 %)	7 (39 %)	5 (38 %)	0 (0 %)	29 (40 %)
Diagnosis						
HD	8 (42 %)	4 (22%)	5 (28 %)	3 (23 %)	1 (20 %)	21 (29 %)
NHL	3 (16 %)	8 (44%)	5 (28 %)	1 (8 %)	0 (0 %)	17 (23 %)
CTCL	**8 (42 %)**	**6 (33%)**	**8 (44 %)**	**9 (69 %)**	**4 (80 %)**	**35 (48 %)**
CTCL Stage¶	**n=8**	**n=6**	**n=8**	**n=9**	**n=4**	**n=35**
I a	0 (0 %)	1 (17%)	1 (13 %)	0 (0 %)	0 (0 %)	2 (6 %)
I b	1 (13 %)	1 (17%)	0 (0 %)	3 (33 %)	1 (25 %)	6 (17 %)
II a	1 (13 %)	0 (0%)	2 (25 %)	0 (0 %)	1 (25 %)	4 (11 %)
II b	1 (13 %)	1 (17%)	0 (0 %)	3 (33 %)	1 (25 %)	6 (17 %)
III	2 (25 %)	2 (33%)	2 (25 %)	1 (11 %)	0 (0 %)	7 (20 %)
IV a	2 (25 %)	1 (17%)	3 (38 %)	2 (22 %)	1 (25 %)	9 (26 %)
IV b	1 (13 %)	0 (0%)	0 (0 %)	0 (0 %)	0 (0 %)	1 (3 %)
Dx Duration(yr)	**n=8**	**n=6**	**n=8**	**n=9**	**n=4**	**n=35**
Mean ± SD	2.7 ± 2.1	4.1 ± 3.9	2.8 ± 2.5	5.1 ± 4.2	2.8 ± 2.0	3.6 ± 3.1
Range	0.7 - 7.2	0.7 - 11.7	0.6 - 7.9	0.2 - 12.0	1.1 - 4.9	0.2 - 12.0

¶ Patients with CTCL only

MTD

The maximum tolerated dose in this study was 27 µg/kg/day for 5 days. Four of the 5 patients enrolled in the 31 µg/kg/d dose level cohort withdrew for adverse events. Dose-limiting toxicities consisted of persistent, moderate and severe nausea, vomiting, fever, chills and asthenia.

Response Rate and Duration in Non-CTCL Patients

There were no responses observed among the 21 patients with HD. There were 3 responses (1 CR and 2PR) among the 17 patients with NHL. There were 2 responses among 7 patients with low grade NHL, 1 of 6 patients with intermediate grade and 0 of 4 with high-grade histology. The response durations were 2, 9, and 20+ months.

Response Rate and Duration in CTCL Patients

(i) ———————————

3 Citrate equivalent doses, based upon mass as measured by ——— rather than the BCA method, are provided for all patients. Citrate equivalent doses in µg/kg/d ——— are provided in parentheses for each of the dose level cohorts: 150 kU/kg/d (3); 300 kU/kg/d (6); 450 kU/kg/d (9); 600 kU/kg/d (12); 750 kU/kg/d (15); 900 kU/kg/d (19); 25 µg/kg/d BCA (19); 1050 kU/kg/d (23); 30 µg/kg/d BCA (23); 35 µg/kg/d BCA (27); 40 µg/kg/d BCA (31)

Thirteen of the 35 patients (37%) with CTCL in this study achieved an objective tumor response; there were 5 complete responses and 8 partial responses reported by the clinical investigators. The duration of responses ranged from 2.6 to 22.7+ months, with a median duration of response of 7.3 months (see Table 6). Four of the five complete responders were in remission at the time of the last contact, with ongoing responses at 8, 13, 15, and 23 months. There was no evidence of a dose-response relationship. Responses were observed at dose levels of 6 through 27 µg/kg/day.

TABLE 6: Summary of Response Rates and Duration for CTCL Patients

Response group	Response rate	Median duration (mos) [25th, 75th quartiles]
Overall	37% (13/35)	7.3 (3.1; 19.9)
Complete	14% (5/35)	16.6 (ND*, 16.6)
Partial	23% (8/35)	3.1 (3.0, 6.1)

* ND = Not Determined

The majority of the responses were observed in patients with early stage disease (Table 7). The overall response rates were 50-60% for patients with stage Ia through IIb disease as compared to 29% (2 of 7 patients) for Stage III and no responses reported in the 10 patients with Stage IV. Because there were also relatively fewer patients with advanced (Stage III and IV) disease enrolled at the higher dose levels, it cannot be determined whether the lower response rate in advanced stage disease may, in part, be explained by inadequate dose-intensity.

TABLE 7: Response Rates by CTCL Stage

Stage	# pts w/ CR	# pts w/ PR	ORR
Ia	2	0	66% (2/3)
Ib	1	2	60% (3/5)
IIa	0	2	66% (2/3)
IIb	1	3	58% (4/7)
III	1	1	29% (2/7)
IVa	0	0	0% (0 /9)
IVb	0	0	0% (0/1)
Total (n=35)	5/35 (14%)	8/35 (23%)	**13/35 (37 %)**

The clinical characteristics of patients with objective clinical responses according to citrate equivalent dose, stage and duration of disease, extent of prior treatment, response (CR vs. PR) and duration of response to treatment are summarized in Table 8 below.

TABLE 8: Characteristics of CTCL Patients with Objective Responses

Dose Level (μg/kg/d)	CTCL Pts in dose level	Pt No.	No. Prior Therapies	Disease Duration (years)	Disease Stage	Response	Duration of Resp. (months)
6	2	204	3	2.5	II b	PR	6.3
9	6	705	1	0.7	III	PR	3.4
12		211	2	2.0	II b	PR	3.0
12	3	508	2	2.1	I a	CR	>22.7
12		722	15	11.7	I b	PR	19.9
15	3	527	2	3.9	III	CR	16.6
19		217	3	4.3	II a	PR	3.1
19	8	520	2	1.8	II a	PR	3.1
19		538	3	8.0	I a	CR	> 15.1
23	6	554	1	0.9	I b	CR	> 13.2
27		416	2	unknown	II b	PR	7.3
27	3	550	0	0.3	I b	PR	2.6
27		558	6	6.9	II b	CR	>8.0

There were no responses observed at the highest dose level (3 1 μg/kg/d) in which 4 patients with CTCL were enrolled. There were 1 - 18 patients enrolled per study site and between 1 and 12 CTCL patients enrolled at 8 of the 9 study sites. (see Appendix 1). Responses in patients with CTCL were reported at 7 of the 8 sites which enrolled CTCL patients.

Subset Analyses (Secondary Analyses)

Twelve of the 35 patients with CTCL (34%) completed all 6 cycles of therapy and were considered by the sponsor to be "evaluable". Nine of the 12 "evaluable" patients responded to therapy. There were four patients with CTCL enrolled in this study that had previously received DAP_ IL-2. Two of the 4 patients achieved a partial response.

Safety Summary

All 73 patients experiencedclinical adverse events (AE's) as well as laboratory AE's. (Table 9) The toxicity profile was characterized by fever and chills in 85% of the patients. accompanied by other constitutional symptoms (asthenia, anorexia. and malaise) in 30-80% of the patients. Among the 1047 clinical adverse events reported. there were 82 (8%) Grade 3 and 9 (1%) Grade 4 clinical adverse events. The incidence of Grade 3 - 4 adverse events was higher at doses above 15 μg/kg/day for the following clinical AE's: chills/fever, asthenia. malaise, anorexia and nausea/vomiting (Table 10).

TABLE 9:Patient Incidence (≥ 5%) of Clinical AE's by Organ-System & Dose

System	Citrate-Equivalent dose DAB389IL-2 (µg/kg/d)					All patients
	3 - 9 N = 19	12 - 15 N = 18	19 N = 18	23 - 27 N = 13	31 N = 5	N = 73
Body as a whole						
Chills / Fever	79 %	78 %	83 %	100 %	100 %	85 %
Asthenia	42 %	61 %	67 %	54 %	80 %	58 %
Anorexia	32 %	17 %	28 %	31 %	40 %	27 %
Malaise	0 %	17 %	11 %	15 %	60 %	14 %
Weight loss	5 %	11 %	22 %	23 %	0 %	14 %
Sweat	0 %	22 %	11 %	23 %	0 %	12 %
Dehydration	11 %	6 %	11 %	15 %	0 %	10 %
Flu Syndrome	5 %	11 %	17 %	8 %	0 %	10 %
Insomnia	11 %	6 %	0 %	0 %	20 %	5 %
Nervous System						
Pain	53 %	44 %	50 %	31 %	0 %	42 %
Headache	21 %	33 %	22 %	15 %	20%	23 %
Dizziness	21 %	22 %	11 %	15 %	0 %	16 %
Paresthesia	0 %	22 %	11 %	8 %	20 %	11 %
Anxiety	0 %	6 %	6 %	0 %	40 %	5 %
Rigid Neck	11 %	0 %	11 %	0 %	0 %	5 %
Nervousness	11 %	6 %	6 %	0 %	0 %	5 %
Cardiovascular						
Hypotension	58 %	33 %	78 %	62 %	20 %	55 %
Edema	32 %	61 %	39 %	38 %	40%	42 %
Vasodilation	21 %	39 %	22 %	15 %	20 %	25 %
Chest Pain	11 %	28 %	11 %	8 %	20 %	15 %
Chest Tightness	0 %	22 %	17 %	8 %	20 %	12%
Tachycardia	11 %	0 %	17 %	15 %	40 %	12 %
Hypertension	21 %	0 %	6 %	23 %	0 %	11 %
Respiratory						
Cough Increase	26 %	33 %	22 %	31 %	40 %	29 %
Dyspnea	21 %	39 %	17 %	23 %	40 %	26 %
Lung Disease	5 %	0 %	0 %	23 %	0 %	5 %
Gastrointestinal						
Nausea/Vomiting	53 %	67 %	78 %	69 %	80 %	67 %
Diarrhea	32 %	17 %	17 %	15 %	20 %	21 %
Dyspepsia	0 %	22 %	6 %	0 %	40 %	10 %
Constipation	11 %	11 %	0 %	8 %	0 %	7 %
Infectious Disease						
Infection	53%	39 %	39 %	31 %	20 %	40 %
Rhinitis	21%	22 %	11 %	8 %	20 %	16 %
Pharyngitis	21 %	11 %	17 %	0 %	0 %	12 %
Conjunctivitis	0 %	11 %	11 %	0 %	0 %	5 %
Sinusitis	11 %	6 %	0 %	8 %	0 %	5 %
Dermatological						
Rash	53 %	39 %	17 %	15 %	20 %	32 %
Pruritus	26 %	22%	17 %	15 %	0 %	19 %
Iniection Site Rx	16 %	11 %	0 %	0 %	0 %	7%
Musculoskeletal						
Myalgia	16%	11 %	11 %	15 %	0 %	12 %

TABLE 10: Per-Patient Incidence of ≥ Grade 3 AE's by Organ-System and Dose

System	Citrate-Equivalent Dose DAB389IL-2 (µg/kg/d)					All patients
	3 - 9 N = 19	12 - 15 N =18	19 N = 18	23 - 27 N = 13	31 N = 5	N = 73
Body as a whole						
Chills / Fever	5 %	6 %	0 %	23 %	20 %	10 %
Asthenia	0 %	0 %	11 %	31 %	60 %	12 %
Dehydration	0 %	6 %	11 %	15 %	0 %	7 %
Malaise	0 %	6 %	0 %	8 %	40 %	5 %
Anorexia	0 %	6 %	0 %	8 %	20 %	4 %
Weight loss	0 %	0 %	0 %	8 %	0 %	1 %
Sweat	0 %	0 %	6 %	0 %	0 %	1 %
Allergic Reaction	0 %	0 %	6 %	0 %	0 %	1 %
Anaphylaxis	0 %	0 %	6 %	0 %	0 %	1 %
Insomnia	0 %	0 %	0 %	0 %	20 %	1 %
Nervous System						
Pain	5 %	6 %	11 %	8 %	0 %	7 %
Confusion/A.M.S	0 %	0 %	0 %	8 %	20 %	3 %
Syncope	0 %	0 %	0 %	8 %	0 %	1 %
Headache	0 %	%	6 %	%	0 %	1 %
Cardiovascular						
Hypotension	0 %	6 %	11 %	8 %	0 %	5 %
Atrial Fib	11%	0 %	6 %	0 %	0 %	4 %
Edema	0 %	0 %	6 %	8 %	0 %	3 %
Chest Pain	0 %	0 %	6 %	0 %	0 %	1 %
Chest Tightness	0 %	6 %	0 %	0 %	0 %	1 %
Thrombosis-DVT	5 %	0 %	0 %	0 %	0 %	1 %
Respiratory						
Dyspnea	11 %	6 %	11 %	8 %	20 %	10 %
Pleural Effusion	0 %	0 %	0 %	15 %	0 %	3 %
Pulm. Edema	0 %	0 %	6%	0 %	0 %	1 %
Bronchiolitis	0 %	0 %	6%	0 %	0 %	1 %
Cough Increase	0 %	0 %	0 %	0 %	20 %	1 %
Lung Disease	5 %	0 %	0 %	0 %	0 %	1 %
Gastrointestinal						
Nausea/Vomiting	5 %	0 %	6 %	23 %	20 %	8 %
Dyspepsia	0 %	0 %	6 %	0 %	0 %	1 %
Constipation	0 %	0 %	0 %	8 %	0 %	1 %
Infectious Disease						
Infection	16 %	17 %	6 %	8 %	20 %	12 %
Sinusitis	0 %	6 %	0 %	0 %	0 %	1 %
Dermatological						
Rash	5 %	0 %	6 %	0 %	20 %	4 %
Pruritus	0 %	0 %	0 %	8 %	0 %	1 %
Musculoskeletal						
Muscle Spasms	0 %	6 %	6%	0 %	0 %	3%
Endocrine						
Hyperthyroidism	0 %	0 %	6 %	0 %	0 %	1 %

Hypotension was observed in 55% of the patients; this will be described in more detail below. A vascular leak syndrome characterized by the triad of hypotension, edema and hypoalbuminemia

was reported in 6 patients with CTCL. Other toxicities which appeared to be drug-related included dyspnea and cough (possibly related to the vascular leak syndrome), headache, nausea, diarrhea, transaminase elevations, increased serum creatinine, and anemia. The most common laboratory abnormalities were hypoalbuminemia (86%) and transaminase elevations (62%). The incidence of Grade 3 - 4 V hypoalbuminemia and transaminase elevations were similar (14% vs. 15%); only the former appeared to be associated with morbidity.

Allergic reactions: Hypersensitivity-type reactions, which included wheezing, shortness of breath, chest tightness, anaphylaxis, or any symptom for which epinephrine was administered to a patient, were reported in 15 (2 1 %) patients. These reactions occurred on the day of dosing but did not commonly recur on rechallenge (positive rechallenge in 3 patients). Treatment was discontinued in one patient for a hypersensitivity reaction.

Hypotension: Forty patients (55%) experienced hypotension. In 14 patients, the hypotension was reported during or within hours of the infusion. In 23 of the patients (32% of the total population), fluid resuscitation was required (systolic BP $\leq$ 90 mmHg and/or diastolic $\leq$ 50 mmHg) or the hypotension was associated with other sequelae (edema in 5 patients or hypoalbuminemia in 9 patients). Hypotension was associated with a hypersensitivity-type reaction in 2 patients.

Rash: There were 45 reports of rash among 23 patients; recurring episodes of rash were observed in 10 of the 23 patients. The incidence of rash was highest in patients with Hodgkin's disease, with reports of rash in 10 of 2 1 patients with HD (48%), 10 of 35 with CTCL (29%), and 3 of 17 with NHL (18%). Fifteen of the 23 patients reported rash during the first cycle. A variety of skin eruptions were reported: generalized (56%), maculopapular (27%), urticarial (16%) or petechial (2%). The time to onset of rash was variable, more commonly reported as a delayed toxicity (week after dosing) for patients with rash during cycles 1 and 2, and during dosing for patients with rash on subsequent cycles.

Medical intervention for AE's: Concomitant medication usage was common. Analgesic use (for pain, fever, headache. and prophylaxis of flu-like syndrome) was reported in 69 (95%) patients. Systemic antihistamines use (as premedication to prevent or for treatment of pruritus. chills, fever or as treatment of allergic reactions) was reported in 53 (73%) patients. and antiemetics use was reported in 30 (4 1 %) patients. Medical intervention for the treatment of clinical adverse events was common. Seventy-percent of patients who experienced fever and/or chills received medication, usually acetaminophen but three patients received narcotics (Demerol and Dilaudid). Sixty-one percent of patients with nausea ± vomiting received anti-emetics, 33% of patients with hypotension received intravenous fluid resuscitation, and 32% of patients with edema were treated with diuretics.

Adverse Events by Cycle

The incidence of clinical AE's and the incidence of grade 3 and 4 AE's were higher during the first and second cycles as compared to later cycles. (Table 11) The most frequent AE's, reported

> 30% of patients in cycles 1 - 4, were fever and/or chills, nausea and/or vomiting, asthenia, hypotension, edema, infections, pain, and rash. The incidence of fever/chills asthenia, and nausea/vomiting decreased markedly after the first 2 cycles, whereas the incidence of infection (15-20%), pain, headache, vasodilatation, dyspnea, and rash were similar across all cycles.

TABLE 11: Per-patient Incidence (≥ 5%) of Clinical AE's by Cycle and Organ-System

System	Treatmeat Cycle Number (n = patients treated per cycle)							
	1	2	3	4	5	6	7	8
	N = 73	N = 52	N = 39	N = 27	N = 22	N = 20	N = 6	N = 6
Generalized								
Chills/Fever	75 %	60 %	44 %	41 %	23 %	15 %		17 %
Asthenia	49 %	29 %	13%	11 %	5 %	5 %		
Anorexia	22 %	12 %						
Malaise	11 %							
Dehydration	5 %							
Sweat		8 %	5 %		5 %	5 %		
Weight Loss		8 %	5 %	11 %				
Flu Syndrome						5 %		
Lymphadenopathy						5 %		
Nervous System								
Pain	23 %	21 %	26 %	11 %	23 %	15 %		17 %
Headache	15 %	12 %	5 %		9 %	10 %		
Dizziness	8 %	10 %	5 %	7 %	9 %			
Paresthesia	7 %		5 %					
Anxiety	5 %							
Depression						5 %		
Emotional Lability						5 %		
Cardiovascular								
Hypotension	34 %	25 %	23 %	22 %	23 %	5 %	17 %	17 %
Edema	33 %		10 %		14 %	10 %	17 %	
Chest Pain	8 %		5 %	7 %				
Tachycardia	8 %	6 %						
Vasodilatation	7 %	17 %	15 %	7 %	14 %	15 %	17 %	17 %
Hypertension	5 %		8 %	7 %	5 %	15 %	17 %	
Chest Tightness		8%			14 %	10 %		
Bradycardia			5 %					
Atrial Fibrillation					5 %			
Phlebitis								17 %
Respiratory								
Dyspnea	16 %	6 %	5 %	7 %	14 %	5 %		17 %
Cough Increase	15 %	12 %	10 %	7 %	14 %			
Bronchitis					5 %			
Gastrointestinal								
Nausea/Vomiting	49 %	46 %	23 %		9 %	10 %		17 %
Diarrhea	14 %	8 %			5 %			
Dyspepsia	5 %					5 %	17 %	
Constipation					5 %			
Dysphagia								

TABLE 11 (continued)
Per-Patient Incidence (≥ 5%) Clinical AE's by Cycle and Organ-System

System	Treatment Cycle (N = patients treated per cycle)							
	1	2	3	4	5	6	7	8
	N = 73	N = 52	N = 39	N = 27	N = 22	N = 20	N = 6	N = 6
Infectious Disease								
Infection	22 %	19 %		19 %	5 %	10 %	17 %	
Rhinitis	10 %	13 %	8 %	7 %		15 %	17 %	
Pharyngitis	8 %				5 %	5 %		
Sinusitis		6 %						
Conjunctivitis					5 %			
Dermatological								
Rash	21 %	15 %	18 %	11 %	5 %	10 %	17 %	
Pruritus	11 %	8 %	5 %		5 %	10 %		
Injection Site Rx			5 %					17 %
Mucous Memb. Dz					5 %	5 %		
Musculoskeletal								
Myalgia	7 %	8 %	8 %					
Muscle Cramps			5 %		5 %	5 %	17 %	17 %
Genito-urinary								
Urinary Urgency					5 %	5 %		

Deaths on study

There were two deaths within 30 days of study drug and two additional deaths within 40 days of study drug. The two on-study deaths were due to progressive ARDS and pulmonary failure in a recent transplant recipient and to disseminated intravascular coagulation (DIC) in a patient with intercurrent CMV and *S. aureus* catheter-related sepsis. The other deaths were attributed to progression of the underlying malignancy. For additional details, see the Integrated Safety Summary.

Discontinuation of study drug due to adverse events.

Twelve patients discontinued therapy for adverse events. These included fatigue and/or anorexia in 5 patients and atria1 fibrillation, hypersensitivity reaction, exacerbation of BCNU-pulmonary toxicity, hypoalbuminemia. anemia, eosinophilia. and decreased performance status in one patient each. One patient who had discontinued treatment for a generalized maculopapular rash treated with oral steroids resumed therapy nine months later without recurrence of rash.

Serious adverse events:

There were 23 reports of serious and unexpected adverse events. Three of these AEs had not been reported in previous trials. These three were new onset atria1 fibrillation in a 77 year old woman with CTCL and no history of cardiac disease (this patient discontinued therapy), ARDS in a 27 year old male with HD who died (described above), and aseptic meningitis of delayed onset in a 25 year old male with CTCL. Aseptic meningitis did not recur during any of three additional cycles of treatment in this subject. There were 20 reports of serious, adverse events

requiring hospitalization for AEs that had been previously reported. These included pneumonia in 4 patients, sepsis in 4 patients (all with CTCL), anemia in 3 patients, dyspnea in 2 patients, hypotension in 2 patients, and one patient each with anaphylaxis, vomiting, Ludwig's angina, anorexia, bronchiolitis, headache, constipation (secondary to narcotic use), fever, Herpes zoster, eosinophilia, pain (related to progressive tumor), syncope, and DVT. Although most of the serious adverse events did not recur with retreatment, anemia was observed to recur in 2 of the 3 patients who were rechallenged.

There were nine grade 4 clinical adverse events. These were infection (n=3), dyspnea (n=2), dehydration (n=l), asthenia (n=1), and emesis (n=l). The incidence of grade 3 clinical adverse events in descending order was: asthenia (11%); fever (10%); infection (8%); pain, emesis and dyspnea (7% for each), hypotension, malaise, and dehydration (5% for each); rash and anorexia (4% each); and edema (3%). There was one episode of each of the following grade 3 adverse events (1% incidence): cough, headache, pruritus, chest pain, chest tightness, weight loss, sweating, and dyspepsia.

Immunogenicity:
Twenty-seven (38%) of the 7 1 patients with baseline data had evidence of a pre-existing immune response (detectable serum antibody of ≥ I :25 to diphtheria toxin (DT) or DAB – L-2) at the time of study entry. Ninety-two percent of patients were found to detectable serum titers after two cycles. The sponsor reports that, following two-cycles, 70% of the patients had a 25-fold increase in the antibody titer compared to baseline.

(3) Protocol 93-04- 10
Protocol Synopsis
Title: A Multicenter Phase III Blinded, Randomized Study to Evaluate the Safety. Efficacy and Pharmacokinetics of Two-Dose Levels of $DAB_{389}IL\text{-}2$ (9 and 18 μg/kg/d) in Cutaneous T-cell Lymphoma (CTCL) Patients with Stage Ib to III Disease Following ≥ 4 Previous Therapies. or Stage IVa Patients Following ≥ 1 Previous Therapy. Who Have Recurrent or Persistent Disease

Study Design: A multicenter Phase III blinded. randomized study to evaluate the safety. efficacy. and pharmacokinetics of two dose-levels of $DAB_{389}IL\text{-}2$ (9 and 18 μg/kg/d) in cutaneous T-cell lymphoma (CTCL) patients. Stratification by disease stage (≤ IIa. ≥ IIb).

Objectives:
- To demonstrate efficacy assessed by the frequency and duration of CRs and PRs.
- To assess changes in symptoms and functional status in association with therapy.
- To further evaluate the safety and tolerability of therapy with these doses and schedules.
- To further characterize the pharmacokinetics of the therapy in these patients.

Inclusion Criteria: Histological confirmation of CTCL with IL-2 receptor expression (with CD25+ expression in ≥ 20% of the cells of either tumor tissue or circulating cells). CTCL disease

Stage I b to IV a (a modification of the TNM Classification by Bunn, combined with the LN staging system by Sausville); ECOG PS of O-2 and at least 14 days since last anti-cancer therapy

Exclusion Criteria: Active infection requiring parenteral antibiotics or amphotericin; significant pulmonary symptoms/disease; uncontrolled seizure or active CNS disease; NYHA class III or IV; poorly controlled HTN; > 20% circulating abnormal lymphocytes.

Treatment Plan:

- 9 or 18 μg/kg/d $DAB_{389}IL\text{-}2$ intravenously over 15 to 60 minutes daily x 5 every 2 1 days for a maximum of 8 cycles
- Premedications: Tylenol 650 mg prior to infusion
- Dose modifications: None. Patients with dose-limiting toxicity were to discontinue therapy

Tumor response criteria; The following response criteria were used in assessment of patients in this study (also in Protocols 93-04-l 1 and 93-04-14). Tumor assessment was performed after every cycle (approximately every 3 weeks). Each tumor measurement was compared with the baseline values and expressed as a percent change from baseline. The initial response to therapy is confirmed by 2 additional assessments over a period of at least 6 weeks during the treatment phase of the study.

- Complete response (CR): No evidence of active disease clinical based on tumor assessment, and histopathology indicates absence of atypical cells.
- Complete response (CR): No evidence of active disease clinical based on tumor assessment, and histopathology demonstrates atypical cells.
- Partial response (PR): A reduction in measured tumor burden of 250% compared with baseline, stable over 3 consecutive assessments over at least 6 weeks.
- Stable disease (SD): ≤25% increase or <50% decrease in measurable disease. no new lesions
- Progressive disease (PD): ≥ 50% increase in measured tumor burden; or appearance of new lymph nodes (CTCL histopathology documented ≥ LN3); or for patients with minimal skin involvement ≤ 10% BSA), new skin lesions in > 2 sites; or development of visceral disease.

The following procedure was used for determination of tumor burden (the same procedure will be used in the supportive studies, Protocols 93-04-l 1 and 93-04-14).

Tumor Burden Assessment (recorded by clinical investigators)

- Skin: weighted extent and severity score or bidimensional measurements of target lesions[4]

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4 For patients with < 10% of the body surface area (BSA) involved, then up to 5 lesions were identified at baseline and measured in 2 dimensions using a transparent plastic grid (counting the no. of squares the lesion fills). The final reported values were weighted, dependent upon the type of lesion (1 = patch. 2 = plaque, and 4 = tumor). The percentage change in the weighted sum of the products of the perpendicular diameters (measured in cm^2) was used to evaluate changes in skin tumor burden.

For patients with ≥ 10% of the BSA involved, a standardized figure on the clinical disease assessment case report form was used. upon which an assessor drew the patient's skin lesions. Different symbols were used to

- lymph nodes(measured in patients with ≥ LN3 classification' at baseline): sum of the measurement of the perpendicular diameters in up to 5 representative nodes ≥ 1cm^2 identified at baseline and measured serially
- blood (assessed in patients with ≥ 20% circulating atypical lymphocytes): serial measurement of the abnormal lymphocyte counts (1 0^3 cells/μl)

Tumor burden was calculated separately for skin, lymph nodes, and blood. The percentage change in tumor burden was based upon comparison to baseline values and reported as the average of the percent change in skin plus the percent change in nodes plus the percent change in blood.

Secondary Endpoints

1. Quality Of Life (QOL) assessment tools developed for psoriasis and a topic dermatitis studies were used to capture changes in disease related symptoms in a quantitative manner. The objective and subjective QOL tools used in the study were:
   - The Physician's Erythroderma Severity Assessment
   - The Physician's Global CTCL Severity Assessment
   - The Patient's Global CTCL Skin Assessment
   - The Patient's Pruritus Visual Analog Scale
2. Use of rescue medicines to ameliorate symptoms of CTCL [included Atarax (hydroxyzine), Aquaphor, Eucerin, and Aveeno (oatmeal) bath], was recorded at baseline (7-14 days prior to the first infusion) and prior to each cycle.

Analytic Plan

The primary efficacy analysis was the overall response rate (as determined by the Data Endpoint Review Committee [DERC][6] with determination of the 1 -sided and 2-sided 95% confidence intervals around the overall response rate (ORR), performed in the intent-to-treat population. The primary analysis was to be performed when two-thirds of the patients had been followed for nine (later amended to six) months after the last dose of drug.

The sample size of 64 patients was selected to permit detection of a 35% difference in the rate of

(i) ———————————————

denote patch, plaque, or tumor lesions. A standardized grid was placed over the figures and the number of cross-points over each drawn lesion were counted. Each set of symbols was performed 3 times, recording the separate counts, and then an average of the 3 separate counts for each set of symbols was determined. The average was then weighted dependent upon the type of lesion (1 = patch. 2 = plaque, and 4 = tumor). The percentage change from baseline in the weighted extent and severity score component of the index was used to evaluate the percentage change in skin tumor burden.

5 LN3 = atypical lymphocytes arranged in ggregates with nodal architecture preserved
LN4 = partial or complete replacement of nodal architecture by atypical lymphocytes

6 5 physicians, divided into two teams (1 oncologist and 1 dermatologist per team) and one referee (a dermatologist)

adverse events between the two dose groups with a power of 84% and α= 0.05.

Secondary efficacy analyses:

1. Overall response rate in two subsets:
   a. Efficacy: All patients who received at least one dose of $DAB_{389}IL\text{-}2$.
   b. Evaluable patients: Patients, who satisfied all pre-study entry criteria, did not receive any concomitant anticancer therapy, had baseline and post-treatment evaluation of response, and received all 8 infusions
2. Complete response rate
3. Response duration, defined as the interval from date of first observation of response to date of relapse or initiation of new anti-cancer treatment;
4. Improvement in clinical symptomatology:
   a. Improvement in at least one integer in the patient global assessment
   b. If present at baseline, improvement in pruritus by at least 20% on the PVAS
5. Decrease in utilization of rescue medications
6. Time to treatment failure (TTF) defined as the interval from date of first infusion until the date of relapse, new anti-cancer treatment, progressive disease, or toxicities requiring discontinuation of therapy.

Protocol Revisions

1. April 6, 1995
   - Eliminate hydrocortisone cream as a rescue medication.
   - Include topical steroids (of any strength) as exclusionary.
   - Specify that patients are to refrain from topical rescue medications $\geq$ 12 hours prior to tumor burden assessments.
2. October 23, 1995
   - Clarify the definition of "documented response".
   - Modify the requirements and timing for skin and lymph node biopsies.
   - Permit the investigators to review Grade 4 toxicities with the medical monitor.
   - Clarify exclusionary active infections.
   - Exclude patients with a recent history of cancer.
   - Clarify the entry criteria for renal function.
   - Decrease the acceptable entry limits for hemoglobin and hematocrit.
   - Clarify which aminoglycosides are exclusionary.
   - Modify the flowchart for Sezary patients.
   - Modify the requirements for follow-up skin biopsies.
   - Clarifying cross-referencing in Section 8.3.2.
3. February 19, 1996
   - Increase the minimum platelet count from >50,000 to > 100,000 for study entry.
   - Clarify exclusion of patients with bone marrow. liver or spleen involvement.
   - Specify safety parameters for continued dosing.
   - Require a complete blood count. chemistries, and urinalysis at Days 10 and 18 visits.

- Add a Day 10 visit (physical exam, weight, vital signs and laboratory evaluation),
- Add a physical examination at Day 18.
- Expand testing to include glucose, bicarbonate, LDH isoenzymes and haptoglobin levels.
- Modify the pharmacokinetic sample times.
- Modify the requirements and timing of lymph node biopsies.
- Clarify the recommended infusion time.
- Require the administration of pre-infusion medications.
- Add pyruria to the toxicity grading table.

Results:

Patient Disposition

There were 71 patients enrolled in the study at 20 centers. Thirty-five patients were randomized to the 9μg/kg dose and 36 patients to the 18 μg/kg dose group. All patients completed at least one cycle of therapy and 30 patients (42%) completed all 8 planned cycles of treatment. Among the 41 patients who failed to complete all planned treatment, 26 patients (37%) discontinued treatment for adverse events, 5 patients (7%) discontinued treatment due to progressive disease, 5 discontinued treatment due to patient withdrawal of consent, 3 (4%) discontinued for worsening symptoms, 1 patient was determined to be ineligible and one discontinued treatment for "other" reasons, The percentage of patients who discontinued therapy prematurely was similar for the two dose groups (20 of 35 patients in the 9 μg/kg dose level and 2 1 of the 36 patients in the 18 μg/kg dose group dropped out). Among 35 patients in the 9 μg/kg/d group, 11 patients discontinued treatment due to adverse events, 4 for progressive disease, 2 withdrew consent, 2 had worsening symptoms and one was listed as a "protocol violation". Among 36 patients in the 18 μg/kg/d group, 15 withdrew due to adverse events, 1 for progressive disease, 3 withdrew consent, 1 had worsening symptoms and 1 patient for reasons, which were not specified in the application.

TABLE 12: Patient Disposition

	All Pts	9 μg	18 μg
Completed 8 cycles			
Yes	30 (42 %)	15	15
Reason for Study Discontinuation			
Adverse Event(s)	26 (37 %)	11	15
Disease Progression	5 (7 %)	4	1
Withdrawal at patient request	5 (7 %)	2	3
Protocol Deviation	1 (1 %)	1	0
Worse Symptoms	3 (4 %)	2	1
Unspecified	1 (1%)	0	1

Patient Population

The two dose groups were well balanced with regard to baseline entry characteristics. The baseline entry characteristics for all patients and in each dose group are summarized in Table 13. The majority of patients had a clinical diagnosis of mycosis fungoides (MF) (76%). ≥ stage II b

disease (63%), ≥ 4 prior treatment regimens (87%), and skin-only involvement (78%). There were 68 subjects with baseline classification of the extent of cutaneous involvement; of these 68, there were 56 (82%) classified as minimal (<10% BSA) skin involvement. The distribution of racial/ethnic groups is consistent with the prevalence of CTCL in these groups.

TABLE 13: Baseline characteristics for Protocol 93-04-10

	9 μg/kg/d	18 μg/kg/d	Total
Characteristics	**N = 35 patients**	**N = 36**	**N = 71**
Sex, n (%)			
Male	20 (57%)	17 (47%)	37 (52%)
Female	15 (43%)	19 (53%)	34 (48%)
Age, years			
≥ 65 yrs	15 (43%)	20 (56%)	35 (49%)
Median	64.0	65.5	64.0
Range	36 - 90	26 - 78	26 – 90
Race			
Caucasian	28 (80%)	25 (69%)	53 (75%)
African American	5 (14%)	7 (19%)	12 (17%)
Hispanic	2 (6%)	4 (11%)	6 (9%)
Biological Diagnosis			
Mycosis Fungoides	28 (80%)	26 (72%)	54 (76%)
Sézary Syndrome*	7 (20%)	10 (28%)	17 (24%)
Disease Stage, n (%)			
≤ II a	14 (40%)	12 (33%)	26 (37%)
≥ II b	21 (60%)	24 (67%)	45 (63%)
CTCL Duration (yrs)			
< 2.5	10 (29%)	8 (22%)	18 (25%)
2.5 - 5.9	7 (20%)	15 (42%)	22 (31%)
> 5.9	12 (34%)	9 (25%)	21 (30%)
Unknown	6 (17%)	4 (11%)	IO (14%)
Median	4.7	4.7	4.7
Range	0.9 – 15.3	0.3 - 20.2	0.3 - 20.2
No. Prior Txs, n (%)			
1	2 (6%)	1 (3%)	3 (4%)
2 - 3	2 (6%)	4 (11%)	6 (9%)
24	31 (89%)	31 (86%)	62 (87%)

*Based on the presence of erythroderma and ≥ 5% Sezary cells

Primary Efficacy Analysis - DERC assessment of Overall Response Rate (ORR).
The overall response rate was 30%. There were three pathologic complete responses and four clinical complete responses for a combined CR rate of 10% and 14 partial responses (PR) for a partial response rate of 20%. The response rates for the two dose groups were similar; there were 2 CRs, 2 CCRs, and 9 PRs in the 18 μg/kg group (CR 11%, PR 25%, and ORR 36%) and 1 CR, 2 CCRs, and 5 PRs identified in the 9 μg/kg group (CR 9%, PR 14%, and ORR 23%). There were 10 responses (38%) identified among the 26 patients with early stage (≤IIa) disease and 11 responses (24%) among the 45 patients with stages IIb -IV disease. The response rates by dose

group and stage of disease are presented in Table14.

TABLE 14: Response Rate by Dose Group and Stage

Stage	9 μg/kg (N = 35) CR	9 μg/kg (N = 35) PR	18 μg/kg (N = 36) CR	18 μg/kg (N = 36) PR	All (N = 71) ORR
I b	3	1	1	I2	44 % (7 / 16)
II a	0	2	0	0	20 % (2 / 10)
II b	0	1	2	3	32 % (6 / 19)
III	0	0	0	4	36 % (4 / 11)
IV	0	1	1	0	13 % (2 / 15)
Response Rate	9 %	14 %	11%	25 %	30 % (21 / 71)
95% CI	(2-23 %)		3 - 26 %	12-42%	18 - 41%
ORR	23 %		36		30 % (21 / 71)
95% CI	(10 - 40%)		(21 - 54%)		18 - 41%

Secondary Analyses

Sites of involvement in relation to response:

FDA explored the relationship of site(s) of involvement to response; the response rate by site of involvement is presented in Table 15. The majority of patients (55 of the 7 1) enrolled in the study had disease limited to the skin. Patients with only cutaneous involvement accounted for 19 of the 21 responses. One response each was observed among the 9 patients with skin and nodal involvement and the 4 patients with skin and peripheral blood involvement. No responses were observed in the three patients with cutaneous, nodal, and peripheral blood involvement.

TABLE 15: Response by Site (s) of CTCL Involvement

Sites of Disease	9 μg/kg/d n = 35	18 μg/kg/d n= 36	Total n = 71
Skin only	8/29 (24 %)	11/26 (42 %)	19/55 (35%)
Skin/Lymph node	0/3 (0%)	1/6 (17 %)	1/9 (11 %)
Skin/blood	0/1 (0%)	1/3 (33 %)	1/4 (25 %)
Skin/lymph node/blood	0/2	0/1	0/3

Response by center

The treatment effect across centers was assessed by determining the response rates for each of the 6 sites, which enrolled 5 or more patients. There was at least one responding patient at each of the 6 sites; response rates ranged from 17% to 50% at these sites.

Response rate by immunohistochemistry score.

There was no correlation between baseline staining grade and response to the therapy. Of the 21 responders, 7 1% (15 of 2 1) had a staining score of 2 and 14% (3 of 2 1) had a staining score of 3. In the remaining 14% (3 of 21), multiple tumor specimens were examined and the percentage of

tumor cells expressing the CD25 antigen for each of the samples was not provided in the application. The response rates were representative and proportional to the baseline CD25+ scores of the study population (see Section V for details of immunohistochemistry results).

Anti-tumor activity (minor response) in responding and non-responding patients
The optimal duration of therapy is not clear. The median time to onset of response was cycle 2, however objective tumor responses were not observed until cycles 6-8 in a few patients. FDA performed an exploratory analysis of time to onset of a minor response in the 21 patients who ultimately achieved a PR, CCR, or CR. The proportion of patients who achieved at least a 25% reduction in tumor burden (minor response) is tabulated below:

One responding patient # 301 did not have at least 25% decrease in tumor burden until the end of Cycle 6. A minor response was reported after 2 cycles in 86% of the subjects who ultimately achieved an objective response and in 46% of patients who never achieved a documented response. This analysis would suggest that lack of a minor response after 2 cycles is more useful in identification of subjects unlikely to benefit from additional therapy but evidence of minor response is only marginally useful in identification of patients who may benefit from continued therapy

TABLE 16: Patients with ≥ 25% Decrease in Disease Burden

# Cycles Completed	Responders N = 21	Non-responders N = 50
1	10 (48%)	17 (34%)
2	18 (86%)	23 (46%)
3	20 (95%)	28 (56%)
4	20 (95%)	29 (58%)
5	20 (95%)	30 (60%)
6	21 (100%)	30 (60%)
7	21 (100%)	31 (62%)
Total	**21/21 (100%)**	**31/50 (62%)**

Duration of response, Time-to-treatment,failure, and Progression-Free Survival,:
Duration of response was measured from the date of onset of response until the date of relapse, progressive disease, and/or initiation of a new anticancer treatment. The median overall duration of response was 4.4 months (25% - 75% quartiles were 2.6 mos. - 7.9 mos.); the median duration of response in both dose groups was similar [5.7 months (18 μg) vs. 4.3 months (9 μg); p = 0.71. The median duration of response was not significantly different for patients with low (≤ IIa) and high (≥ IIb) tumor stage, [4.8 vs. 4.3 months, respectively (Table 17)]. The time to treatment failure' was similar in the two dose groups, with a median TTF of 4.1 months and 3.5 months in

(i) ———————————

7 Time to treatment failure (TTF) defined as the interval from date of first infusion until the date of relapse, new anti-cancer treatment, progressive disease, or toxicities requiring discontinuation of therapy

the 18 μg/kg and 9μg/kg dose groups, respectively. The sponsor provided an analysis of progression-free survival (PFS), which was also similar between the two dose groups, with median PFS of 5.4 months (18 μg) and 4.2 months (9 μg).

TABLE 17: Response Duration by Low vs. High Stage

	Stage		All Patients
	≤ II a	≥ II b	
Response rate	38% (10/26)	24% (11/45)	30% (21/71)
Median Duration (mos)	4.8	4.3	4.4
25% & 75 % Quartiles (mos)	2.1; 11.6	3.2; 7.2	2.6; 7.9

Factors associated with response:

The sponsor performed a logistic regression analysis to evaluate for factors associated with response. The variables included were gender, age, time from diagnosis, early vs. late stage of disease, number of prior treatment regimens, sites of involvement (cutaneous, nodal, and peripheral blood), and clinical syndrome (mycosis fungoides vs. Sezary syndrome). None of these factors was reported to be significantly associated with response to treatment. This analysis was not performed or confirmed by the FDA.

Symptom Relief:

The study prospectively collected several types of information to assess the effects of therapy on tumor-related symptoms and overall well being. These consisted of three patient assessments tools (the Pruritus Visual Analog Scale [PVAS], the Patients' Global Skin Assessment and a more general quality of life instrument [FACT-G]), two physician assessment tools (Physician's Global Severity Assessment and Physicians' Erythroderma Severity Assessment). and measurement of palliative (rescue) medication use.

The FDA reviewer evaluated the changes in PVAS measurement as an assessment of subjective symptom relief and the change in medication usage as a more objective measurement of tumor-related symptoms. The Patient's Global Skin Assessment scale did not record a baseline value for patient assessment, but asked patients to rate their degree of improvement or worsening based upon their recollection of their status at study entry. This scale was felt be unreliable due to the lack of a baseline value and potential for bias or error in recollection of baseline status. The FACT-G scale was not evaluated due to the relative insensitivity to detection of relevant tumor-related symptoms. The physician assessments were considered to be secondary measures of tumor reduction and not relevant to assessment of improvement in patients' symptomatology.

PVAS

In an exploratory analysis, the proportion of patients with clinically significant changes in PVAS scale and those with changes in medication usage were evaluated for the responding patients for insight into the association between decrease in tumor burden and the change in these measures of symptomatology. Five of the seven patients who achieved CR or CCR had complete resolution of symptoms (PVAS score of 0) by the end of the 4"' cycle which remained stable for

at least 2 cycles (≥ 6 weeks). For the remaining 2 CR/CCR patients, one was relatively asymptomatic at study entry and did not develop symptomatic progression and the other patient's PVAS score did not significantly change (<2 integer). Of the 14 PR patients, 12 were symptomatic at baseline with PVAS scores 12 cm. Six of the 12 symptomatic PR patients had durable and clinically significant reductions in PVAS scores. (Table 18)

TABLE 18: PVAS Response in Patients with CR, CCR, PR

Responders	CR	PR
Response	5/7	6/14
No response	1/7	6/14
Asymptomatic at baseline	1/7	2/14

Palliative (Rescue) Medication Usage

There were four patients with objective tumor responses who also received systemic corticosteroids during the study for a variety of reasons (Table 19). In one patient (# 1106), the initiation of corticosteroid therapy was prior to the onset of the objective tumor response. The FDA reviewer could not rule out the possibility that steroid use contributed to objective tumor response and durable symptom relief, based on temporal relationship to response and the extent and duration of steroid therapy.

TABLE 19: Durable symptomatic Responders Who Used Corticosteroids

Responder	Symptom Relief	Corticosteroid	Reason	Cycle Used
218 (PR)	No	Hydrocortisone	Premed for Amphotericin	C1 D5 x 3 d C1, D5-D7
		Solu-Cortef	Premed for IVIG	C1 D9 x 4 d C1, D9 – D12
1106 (PR)	Yes	Solu-Medrol	Premed for infusion	C3 - 9 D0, all x 4 d (except C5 - 3 d; C9 - 1d) Cycles 3-9D O-4
1119 (PR)	No	Solu-Medrol	Premed for infusion	C3 D4 C4 – 6, D0 – D3 x 4 d
1602 (PR)	Yes	Depo-Medrol	Back pain	C3 D17 x 1 d

There appeared to be an increase in medication use early in the study (cycles one and two) which trended toward a return to baseline use over the ensuing cycles. Other than this trend, there was no consistent pattern to rescue medication usage over the course of the study. Specifically. the symptomatic-responding patients did not consistently discontinue or have a significant decrease in rescue medications at the end of treatment as compared to baseline. (See **Section X. Appendix B** for graphic display of palliative medication usage and PVAS scores in responding patients over the course of therapy).

The usage of rescue medications at baseline and at end of treatment in the 11 patients with objective tumor responseswho also experienced durable symptom relief by PVAS is shown in Table 20. With the exception of patient #1602, there was a consistent decrease in Atarax usage. Use of Aveeno Oatmeal bath was low and also generally decreased in usage over the study. However, only one subject (# 1105) discontinued use of all palliative medications and another (#2605) had reduction but not complete discontinuation of palliative medications, whereas for 9 of the 11 subjects with objective tumor and symptomatic response, use of Aquaphor and Eucerin remained stable or increased during the study.

TABLE 20: Rescue Medicine Use Among Symptomatic Responders; Use at Baseline vs End of Study Visit

Pt. No.	Obj. Tumor Resp.	Hydroxyzine (Atarax) Tablets/ visit	Aquaphor Tubes / visit	Eucerin (cream) Tubes / visit	Oatmeal Bath (Aveeno) Tubes / visit
302	CCR	From 1 to 0	**From 1 to 6**	From 2 to 2	From 0 to 0
320	PR	From 0 to 0	**From 1 to 10**	**From 1 to 12**	From 1 to 0
502	CCR	From 0 to 0	From 0 to 0	**From 0 to 12**	From 0 to 0
503	CR	From 0 to 0	From 0 to 0	**From 0 to 2**	From 0 to 0
518	PR	From 0 to 0	**From 6 to 8**	**From 8 to 24**	From 2 to 0
1105	CR	From 10 to 0	From 5 to 0	From 4 to 0	From 2 to 0
1106	PR	From 38 to 0	**From 2 to 3**	From 4 to 4	From 3 to 0
1601	CCR	From 16toO	From 2 to 2	**From 0 to 2**	From 0 to 0
1602	PR	**From 28 to 100**	From 2 to 1	From 0 to 0	From 6 to 2
2605	PR	From 2 to 0	From 6 to 3	From 3 to 0	From 16 to 0
2720	PR	From 8 to 0	From4 to4	**From 2 to 4**	From 1 to 0

There were no significant differences between the dose groups with regard to the degree of improvement in the tumor-related symptoms by any of the QOL tools and there were no significant differences between dose groups with regard to the degree of change in rescue medication use.

Safety Summary

All clinical adverse events were included regardless of investigator-assessed attribution to therapy. Table 21 lists, by organ-system, the AEs reported in ≥ 5% of the patients. All patients enrolled in the study experienced one or more adverse events. Thirty-nine of the 71 patients (55%) experienced one or more serious adverse events and 26 patients (37%) withdrew from the study for adverse events.

The most common adverse events were asthenia (66%), fever (63%) and chills (62%). Other common adverse events included gastrointestinal symptoms (nausea. vomiting, diarrhea), asthenia, generalized discomfort (headache, myalgias, arthralgias, and back pain), respiratory

symptoms (dyspnea and increased cough), hemodynamic changes (hypotension, vasodilatation, peripheral, facial, and generalized edema, and tachycardia) and hypersensitivity-like reactions,

TABLE 21

Pt. Incidence (≥ 5%) of Clinical AE's by Organ-Systems and Dose-Group

System	DAB389IL-2 (18 µg/kg/d)		
	9 N = 35	18 N = 36	Total N = 71
Body as a whole			
Asthenia	63 %	69 %	66 %
Fever	63 %	64 %	63 %
Chills	63 %	61 %	62 %
Anorexia	31 %	56 %	44 %
Weight Loss	14%	14 %	14 %
Insomnia	11%	14 %	13 %
Malaise	3 %	19 %	11 %
Hypokalemia	14 %	8 %	11. %
Hypoalbuminemia	6 %	14%	10 %
↑ Transaminases	6 %	11 %	9 %
Sweating	9 %	8 %	9 %
Dehydration	3 %	11 %	7 %
Flu Syndrome	6 %	6 %	6 %
Hypocalcemia	6 %	6 %	6 %
Nervous System			
Pain	34 %	33%	34 %
Headache	20 %	36 %	28 %
Dizziness	26 %	28 %	27 %
Paresthesia	23 %	8 %	16%
Confusion	14 %	11%	13 %
Anxiety	11 %	6 %	9 %
Depression	14 %	0 %	7 %
Cardiovascular			
Peripheral edema Edema	23 % 26 %	31 % 22 %	27 % 24 %
Vasodilatation	20 %	17 %	18 %
Hypotension	3 %	25 %	14 %
Chest Pain	17 %	6 %	11 %
Tachycardia	14 %	8 %	11 %
Chest Tightness	6 %	14 %	10%
Respiratory			
Dyspnea	34 %	33 %	34 %
Cough Increased	31 %	17 %	24 %
Lung Disorder	9 %	11 %	10 %
Upper Resp infect	11 %	8 %	10 %
Pulm. Edema	3 %	8 %	6 %
Pneumonia	9 %	3 %	6 %

TABLE 21 (continued)
Pt. Incidence (≥ 5%) of Clinical AE's by Organ-Systems and Dose-Group

Organ system	DAB_{389}IL-2 (µg/kg/d) 9 N = 35	18 N = 36	Total N = 71
Gastrointestinal			
Nausea	57 %	64 %	61 %
Diarrhea	40 %	36 %	38 %
Vomiting	26 %	42 %	34 %
Abdominal Pain	14 %	11 %	13 %
Constipation	9 %	14 %	11%
Dysphagia	6 %	11 %	9 %
Dry Mouth	14 %	0 %	7 %
Infectious Disease			
Infection	34 %	31 %	32 %
Pharyngitis	20 %	25 %	23 %
Rhinitis	14 %	11 %	13 %
Urinary Tract Infection	9 %	14 %	11 %
Sepsis	11 %	11 %	11 %
Herpes Simplex	9 %	6 %	7 %
Conjunctivitis	9 %	9 %	9 %
Otitis extema	9 %	3 %	6 %
Dermatological			
Rash	34 %	19%'	27 %
Pruritus	26 %	17 %	21 %
Face Edema	14%	11 %	13 %
lniection Site Reaction	9 %	8 %	9 %
Maculopapular rash	6 %	11 %	9 %
Skin Carcinoma	3 %	11 %	7 %
Alopecia	9 %	3 %	6 %
Exfoliative dermatitis	9 %	3 %	6 %
Skin ulcer	3 %	8 %	6 %
Subcut. Nodules	3%	8 %	6 %
Musculoskeletal			
Myalgia	26 %	22 %	24 %
Back Pain	20 %	22 %	21 %
Arthralgia	11 %	8 %	10%
Hematology			
Anemia	9 %	14 %	11 %
Leukopenia	6 %	8 %	7 %

Infusional toxicity; Specific constellations of adverse events, as reported in Protocol 92-04-o 1, were also observed in this study. There was a constellation of hypersensitivity-type reactions, usually reported during or within hours of the infusion and consisting of dyspnea, back pain,

hypotension, chest pain and chest tightness. Grade 3 infusional or immediately post-infusional adverse events were reported in 5 patients and led to permanent discontinuation of treatment in four of the five patients. From review of the concomitant medications, use of systemic steroids for treatment of hypersensitivity reactions occurred in several patients.

Constitutional symptoms were reported in 63 of the 71 (89%) patients. These symptoms occurred early in the treatment cycle (days O-12) and consisted of flu-like symptoms, malaise, fatigue, arthralgias and myalgias. The majority of the events were of grade 1 or 2 in severity, although two patients discontinued treatment due to constitutional symptoms.

Vascular leak syndrome (VLS), characterized by hypotension, edema, and hypoalbuminemia, was reported as a specific event in a minority of patients by investigators. There were six patients with Grade 3-4 toxicity as manifestations of VLS; all recovered. However three patients with edema, hypoalbuminemia, or hypotension as the sole adverse event discontinued treatment prematurely due to toxicity. The results of retrospective review by medical consultants to Seragen, in which strict criteria for identification of VLS were applied to patients enrolled in studies 92-04-01 and 93-04-10 is presented in the ISS. (Section VII, page 51)

Infectious events: There were 37 patients with one or more reports of an infectious event. Three patients discontinued treatment due to an infectious adverse event and there were 27 infectious events that were ≥ grade 3 in severity. Infections were more common in patients with advanced disease; infections were reported in 28 patients (62%) with ≥ stage IIb disease and 9 (37%) patients with ≤ stage IIa disease.-Eighteen of the 37 patientshad infections that occurred during the first cycle of $DAB_{389}IL2$ therapy.

Severe adverse events: The incidence of grade 3 and 4 adverse events was slightly higher in the 18 μg/kg/d group. Grade 3 or 4 adverse events were reported in 2 1 (58%) patients receiving 18 μg/kg/d compared to 17 (49%) patients receiving 9 μg/kg/d. The most common grade 3 and 4 adverse events were asthenia (27%), fever (23%). chills (23 %), infection, NOS (20%), dyspnea (18%), nausea (18%). rash (17%), and pain. NOS (15%). The incidence of Grade 3 and 4 adverse events. overall and by dose, is presented in Table 22.

TABLE 22

Per-patient Incidence of Grade 3 & 4 AE by Organ-System and Dose

System	$DAB_{389}IL\text{-}2$ (µg/kg/d)		
	9 N = 35	18 N = 36	Total N = 71
Body as a whole			
Asthenia	26 %	28 %	27%
Chills	23 %	22 %	23 %
Fever	14 %	31 %	37 %
Anorexia	9%	17%	13%
Dehydration	3 %	8 %	6 %
Weight loss	11 %	3 %	7 %
Nervous System			
Pain	17 %	14 %	15 %
Confusion	6 %	11 %	8 %
Cardiovascular			
Chest pain	14 %	0 %	7 %
Hypotension	3 %	11 %	7 %
Edema	11 %	11 %	11 %
Peripheral edema	9 %	6 %	7 %
Respiratory			
Dyspnea	20 %	17 %	18 %
Pulmonary edema	3 %	8 %	6 %
Gastrointestinal			
Diarrhea	6 %	8 %	7 %
Nausea	11 %	25 %	18 %
Vomiting	9 %	17 %	13 %
Infectious Disease			
Infection	23 %	17 %	20 %
Sepsis	11 %	11 %	11 %
UTI	3 %	11 %	7 %
Dermatological			
Face edema	9 %	3 %	6 %
Pruritus	3 %	8 %	6 %
Rash	17 %	17 %	17 %
Skin carcinoma	3 %	8 %	6 %
Musculoskeletal			
Back pain	6 %	11 %	8 %
Hematological			
Anemia	6 %	6 %	6 %

Adverse Events by Cycle

The incidence of adverse events was highest during the first (89%) and second (88%) cycles (Table 23). The most common AE's reported in cycles 1-3, in decreasing order of incidence, were asthenia, chills, fever, nausea. anorexia dizziness, paresthesia. vasodilatation, dyspnea. nausea, diarrhea, vomiting, infections (unspecified) and myalgia. However. there was no evidence of a relative decrease in the incidence of certain types of events between the initial and

subsequent cycles, with a relative stable incidence of dehydration, asthenia, headache, confusion, vasodilatation, peripheral--edema, chest pain, dyspnea, cough, and upper respiratory symptoms across all cycles. This suggests that use, or increased use of premedications, may have no impact on the incidence of some adverse events and/or that tachyphylaxis or that the rapid clearance of Ontak due to immune responses observed in later cycles may not impact all $DAB_{389}IL2$-related toxicity. Notably, paresthesia, tremor and depression were reported only in later cycles.

TABLE 23

Per-Patient Incidence (≥ 5%) of Adverse Events by Cycle and Organ-System

System	Treatment Cycle									
	1	2	3	4	5	6	7	8	9	10
	N = 71	N = 57	N = 46	N = 43	N = 38	N = 37	N = 32	N = 30	N = 7	N = 5
Body as a whole										
Asthenia	52 %	16 %	9 %		11 %	11 %	6 %		14 %	20 %
Chills	47 %	33 %	24 %	9 %	11 %	11 %	6 %			
Fever	42 %	40 %	15 %	12 %		5 %	9 %			
Anorexia	32 %	14 %								
Hypoalbuminemia	9 %	5 %								
Hypokalemia	7 %									20 %
Dehydration	6 %								14 %	
Insomnia						5 %				
Anxiety	5 %									
Weight Loss		7 %								
Nervous System										
Pain	16 %			9 %	5 %	11 %	16 %	7 %		
Headache	14 %	11 %			11 %	5 %	6 %		43 %	20 %
Malaise	9 %									
Dizziness	17 %	9 %	9 %						14 %	
Confusion	7 %	5 %								
Anxiety	6 %									
Paresthesia	6 %	5 %	7 %	5 %					29 %	
Ear Disorder		5 %								
Depression									14 %	
Emotional Lability									14 %	
Somnolence									14 %	
Tremor									14 %	
Cardiovascular										
Chest pain	6 %	5 %							14 %	
Tachycardia	9 %									
Vasodilatation	7 %	7 %	7 %					7 %		
Edema	16 %	9 %								
Peripheral edema	14 %				8 %	5 %	6 %	10 %		
Hypotension		9 %								
Chest tightness						5 %	6 %			20 %
Respiratory										
Dyspnea	16 %	12 %	11%	5 %		5 %	6 %		14 %	20 %
Cough increase	7 %	9 %		9 %		8 %				20 %
Pulm. Disorder						8 %				20 %
Upper Resp. Infection			7 %							20 %

TABLE 23 (continued)
Per-Patient Incidence (2 5%) of Adverse Events by Cycle and Organ-System

System	Treatment Cycle									
	1	2	3	4	5	6	7	8	9	10
	N = 71	N = 57	N = 46	N = 43	N = 38	N = 37	N = 32	N = 30	N = 7	N = 5
Gastrointestinal										
Nausea	41 %	32 %	17 %	5 %		11 %	6 %	7 %	14 %	20 %
Diarrhea	23 %	18 %	15 %		5 %	5 %		7 %	14 %	
Vomiting	20 %	18 %	15 %			5 %				
Constipation	7 %			5 %						
Abdominal pain		9 %				5 %			29 %	
Dysphagia		5 %								
↑ Transaminases	9 %	7 %								
Infectious Disease										
Infection	17 %	7 %	11 %	9 %	8 %	8 %		17 %		20 %
Pharyngitis	9 %		7 %	7 %						
Sepsis		7 %								
Rhinitis		5 %	7 %						29 %	
Urinary Tract Infect.		9 %								
Dermatological										
Face edema	10 %									
Rash	18 %	11 %		7 %	5 %					
Pruritus	10 %				8 %					
Skin disorder									14 %	
Musculoskeletal										
Myalgia	11 %	11 %	7 %	5 %			9 %			
Back pain		16 %	13 %	7 %	8 %	22 %	9 %	13 %		
Arthralgia					5 %	5 %	6 %			
Hematological										
Anemia		7 %	9 %	5 %						

Deaths

There were two patients who died within 30 days of study drug and 3 additional patients who died within 90 days after the last dose of study drug. All five of these patients had experienced serious toxicities during the last cycle of treatment. Summaries of these events are provided in the Integrated Safety Summary.

Discontinuation of study drug due to adverse events

Twenty-six patients (37%) withdrew from the study for adverse events. The adverse events which led to discontinuation of treatment were fever (n=3) and nausea, apnea, congestive heart failure, confusion, dyspnea, hypoalbuminemia, increased vascular fragility, and maculopapular rash in 2 patients each. In the 9 µg/kg/d group, 3 1 % discontinued due to adverse events; resolution of AE's occurred in 9 of 11 patients. Patients without toxicity resolution experienced #1520 thrombocytopenia (#1520) and paresthesia (numbness of a fingertip), pain (in hands), dementia, and tenosynovitis (carpal tunnel syndrome) (patient #2603). In the 18 µg/kg/d group,

42 % discontinued due to adverse events; resolution occurred in 14 of the 15 patients; the exception was patient #520 with skin carcinoma.

Serious adverse events

Thirty-nine of the 71 patients (55%) experienced one or more serious adverse events (SAE's). The following events were reported, in decreasing order of incidence: 6 patients (9%) each reported fever and infection; 5 patients (7 %) each reported skin carcinoma and sepsis; 4 patients (6 %) reported pneumonia. Three (4%) or less patients reported the following: 3 patients (4 %) each of dyspnea, hypotension, rash (unspecified); 2 patients (3 %) each of chest pain, pulmonary edema, myocardial infarction, angina pectoris increased vascular fragility, acute renal failure, urinary tract infection, dehydration, and confusion.

In the 9 µg/kg/d group, 54 % (19 of 35) patients had at least one SAE; resolution of SAE's occurred in all patients except for dyspnea in one patient (#5 17) and hypoalbuminemia in another patient (#1102). In the 18 µg/kg/d group, 56 % (20 of 36) patients had at least one SAE; resolution occurred in all except in two patients (#520 and 2420) with skin carcinoma.

Immunogenicity

After a single course of $DAB_{389}IL\text{-}2$, 84% of the patients in this study (41 out of 49) had developed anti-$DAB_{389}IL\text{-}2$ antibodies. Following the completion of two courses, every patient in this study except one (patient 05 18) had developed anti-$DAB_{389}IL\text{-}2$ antibodies.

Effects on lymphocytes

The effects of DAB_{389} IL-2 on circulating lymphocytes were evaluated by serial assessments of absolute lymphocyte counts. Fifty-one of the 7 1 patients were lymphopenic at study entry; 16 patients had ≥ Grade III lymphopenia at entry. Severe lymphopenia (2 Grade III) was observed in 47 patients during study and in 41 of the 47 during treatment or within 5 days of treatment on the first cycle. Some degree of improvement (recovery to >grade III) was observed in 40 of the 47 severely affected patients at the time of final assessment.

(4) Protocol 93-04- 11

Protocol synopsis

Title: A Multicenter Phase III Blinded, Randomized Study to Evaluate the Safety, Efficacy and Pharmacokinetics of Two-Dose Levels of $DAB_{389}IL\text{-}2$ (9 and 18 µg/kg/d) in Cutaneous T-cell Lymphoma (CTCL) Patients with Stage Ia to III Disease Following ≥ 3 Previous Therapies

Study Design: A double-blind, placebo-control led Phase III study to evaluate the safety and efficacy of two dose-levels of $DAB_{389}IL\text{-}2$ (9 and 18 µg/kg/d) in cutaneous T-cell lymphoma (CTCL) patients with Stages Ia-III disease compared to placebo.

Objectives: To demonstrate efficacy and safety of $DAB_{389}IL\text{-}2$ (18 µg/kg/d and 9 µg/kg/d) in cutaneous T-cell lymphoma (CTCL) patients.

End-points:

- *Primary* – Overall response rate
- *Secondary* – duration of response; time to relapse; symptom improvement; quality of life

Inclusion Criteria: Histological confirmation of CTCL with IL-2 receptor expression (with CD25+ expression in ≥ 20% of the cells of either tumor tissue or circulating cells), as well as CTCL disease Stage I b to IV a; ECOG PS of O-2 and at least 14 days since last anti-cancer therapy

Treatment Plan.

1. Placebo (normal saline) or $DAB_{389}IL\text{-}2$ at 9 or 18 μg/kg/d intravenously over 15 to 60 minutes on days l-5 of a 2 1 day cycle. A maximum of 8 cycles was to be administered.
2. Dose Modifications:

Any abnormality occurring during or after agent administration should be monitored until return to baseline condition, stabilizes or the reason for persistence is determined.

Grade I toxicity – continue to receive treatment at full dose as scheduled.

Grade 2 - 3 ***toxicity*** – continue to receive treatment at full dose at the investigator's discretion allowing upwards of 7 additional days beyond Day 2 1 to allow toxicities to satisfactorily abate.

Grade 4 ***toxicity*** – discontinue the study and follow the patient as appropriate for toxicity resolution. However. if the investigator does not believe the Grade 5 toxicity presents a significant risk and wishes to continue dosing, the investigator needs to contact [redacted] . of [redacted] to discuss the patient's toxicity and eligibility for continuation.

Response criteria: See the sections entitled Tumor Response Criteria, Measurement of Tumor Burden, and Secondary Endpoints under Protocol 93-04- 10.

Analytic Plan:

The sample size of 120 patients was chosen based upon the assumptions that the response rate (ORR) in the $DAB_{389}IL\text{-}2$ arms will be 40% and the response rate in the placebo arm will be 10%. A sample size of 40 patients per arm will permit detection of this difference in response rate between each of the active treatment arms and the placebo arm, by Fisher's exact test, with 84% power and an alpha of 0.05. If the two active arms are combined. the power is increased to 90%.

The final analyses for the primary and secondary endpoints will be conducted when all patients have been followed for 6 months after receiving their last dose of $DAB_{389}IL\text{-}2$. or have withdrawn from the study due to treatment failure, death or toxicity. The data cut-off for analysis of the primary and secondary endpoints is the point in time when two-thirds of all patients have been followed for 6 months after receiving their last dose of $DAB_{389}IL\text{-}2$. or have withdrawn from the study due to treatment failure, death or toxicity.

Preliminary Results:

Patient Disposition --

Seventy-three patients had been enrolled as of Jan. 1997; data from 70 of the 73 patients who had been enrolled at the time of the submission, with the treatment blind unbroken, were provided. Fifteen patients have discontinued treatment for adverse events, nine have discontinued treatment due to disease progression, five patients withdrew consent, and two were withdrawn for "other" reasons. The treatment arm remains masked (i.e., patients receiving placebo and those receiving active drug are not distinguished. Pertinent characteristics of the study population at entry are summarized in Table 24 below.

TABLE 24
Baseline entry characteristics (interim report of 70 patients)

Parameter		**#pt (%)**
Age (yrs)	Median	55
	Range	23 – 84
	> 65 years	21 (29%)
Sex, n (%)	Male	39 (53%)
	Female	34 (47%)
Race, n (%)	Caucasian American	54 (74%)
	African American	17 (23%)
	Other	2 (3%)
CTCL Stage, n (%)	≤ II a	51 (70%)
	≥ II b	22 (30%)
No. Prior therapies, n (%)	≤ 3	71 (97%)
	≥ 4	2 (3%)

Efficacy summary

Preliminary tumor response information as determined by the clinical investigators (not yet confirmed by the DERC) were provided. There have been 18 partial responses identified among 70 patients (ORR and PR 29%).

Safety summary

There have been 603 adverse events reported among 70 patients; 70% were grade 1 or 2 in severity, 145 (24%) were grade 3, 34 (6%) were grade 4 and one event is not ungraded. There were 27 serious adverse events reported among 15 patients and one patient death, which resulted from a second malignancy (summarized below). Fifteen patients have discontinued treatment for adverse events. The toxicity profile is similar to that reported for Protocols 92-04-01 and 93-04-10 (see tables in the Integrated Safety Summary). The incidence of adverse events detected by clinical laboratory monitoring were ALT elevations (52%), AST elevations (46%), hypoalbuminemia (49%), elevated serum creatinine (6%), lymphopenia (52%). 29% with anemia (29%), and thrombocytopenia (3%).

Serious adverse events - -

There were 27 serious adverse events reported in 15 patients (2 1%); these are tabulated below:

- Grade 4 vascular leak syndrome and grade 3 respiratory distress;
- recurrent transient leg and arm paresthesias;
- severe abdominal pain and hypertension;
- pancreatitis;
- syncopal episode, with head trauma, and mental status changes (see dropouts);
- malignant pericardial effusion (see dropouts);
- cellulitis and hyperglycemia (see dropouts);
- fever from day 1 through 6 of cycle 1, no infectious source identified (did not recur with rechallenge; hypoalbuminemia (see dropouts)
- basal cell carcinoma (3 separate lesions) and B2 prostate cancer
- dehydration in patient with vomiting and diarrhea during cycle 1, which worsened post-therapy, requiring IV fluids and resolving by day 10
- hypersensitivity reaction (see dropouts) consisting of pruritic rash, hypotension.

Grade 3 and 4 adverse events

There were 8 patients (13%) with grade 3 and one (2%) with grade 4 increases in ALT, and one patient (2%) with grade 3 AST elevations, 2 patients (3%) with grade 3 and 3 (5%) with grade 4 hypoalbuminemia. and one patient with grade 3 anemia.

Discontinuation of study drug for adverse events

There were 14 patients who discontinued therapy due to adverse events. The reasons for discontinuation of therapy were:

- exacerbation of asthma, in association with back pain, nausea, edema;
- vascular leak syndrome
- exacerbation of asthma, chest tightness, and dyspnea (hypersensitivity reaction)
- urticaria (associated with facial edema) progressive after completion of therapy
- throat tightness during infusion on day 3. cycle 1. in a patient with history of hypersensitivity-reactions on days 1 and 2 of cycle 1. treated with IV Benadryl, IV hydrocortisone. and epinephrine. and associated with pruritic rash
- syncopal episode on day 21 of cycle 3, apparently unwitnessed, with head trauma and subsequent mental status changes (treatment discontinued due to altered mental status)
- malignant pericardial effusion (day 3, course 3); patient presented with dyspnea, CHF/pulmonary edema, bilateral pleural effusions, and renal insufficiency (creatinine increased from 1 .O to 2.0 mg/dl). Pericardial tamponade may have been precipitated by IV hydration; there is insufficient information to determine if patient had some component of vascular leak syndrome as well.
- Gangrene of distal extremity, requiring amputation, arising in an insulin-dependent male with cellulitis of the LLE

- hypoalbuminemia, persistent from cycles 1-3. Baseline albumin was 3.0 mg/dl, during treatment period; albumin remained generally less than 2.0 mg/dl. Patient recovered to baseline albumin level 32 days after the last dose on the third cycle
- dehydration in patient with vomiting and diarrhea during cycle 1, which worsened post-therapy, requiring IV fluids and resolving by day 10
- hypersensitivity reaction (see dropouts) on cycle 2 consisting of pruritic rash, hypotension, nausea, vomiting and diarrhea. During drug administration on cycle 1, patient developed

Deaths on study

Pt #2453 was a 60 year old male with stage Ia CTCL who received 7 cycles of therapy (blind has not been broken). The patient was diagnosed with anaplastic astrocytoma during cycle 7 of treatment and died on day 82 of cycle 7; this was 77 days after the last dose of study drug.

(5) Protocol 93-04- 14

Protocol synopsis

Title: A Multicenter Phase III Open-Label Extension Study to Evaluate $DAB_{389}IL\text{-}2$ in Patients with Cutaneous T-cell Lymphoma (CTCL) Following Protocol 93-04-l 0, Protocol 93-04- 11, or Protocol 92-04-o 1

Study Design: A multicenter, single-arm (18 μg/kg/d) open-label extension study in cutaneous T-cell lymphoma (CTCL) patients who are crossed over from Protocol 93-04- 11 or responded and have relapsed after Protocols 92-04-o 1 and 93-04-l 0.

Objectives: To demonstrate efficacy and safety of $DAB_{389}IL\text{-}2$ (18 μg/kg/d) in cutaneous T-cell lymphoma (CTCL) patients.

End-points:

- *Primary* – overall response rate
- *Secondary* – duration of response; time to relapse; symptom improvement; quality of life

Inclusion Criteria:

- Patients who demonstrated a relapse during the follow-up phase of Protocols 93-04- 10 or Protocol 93-04- 11.
- Patients who had a PD on the placebo arm of the 93-04-l 1.
- Patients who, after 8 cycles of therapy, had SD on Protocol 93-04-l 1.
- Patients who relapsed after an initial response to therapy on Protocol 92-04-01.

Treatment Plan:

1. $DAB_{389}IL\text{-}2$ at 18 μg/kg/d intravenously over 15 to 60 minutes on daily. days l-5 of a 2 1 day cycle. A maximum of 8 cycles is to be administered.
2. Dose Modifications:

Grade I toxicity – continue to receive treatment at full dose as scheduled.
Grade II - III toxicity – continue to receive treatment at full dose at the investigator's discretion allowing upwards of 7 additional days beyond Day 21 to allow toxicities to satisfactorily abate.
Grade IV toxicity – discontinue the study and follow the patient as appropriate for toxicity resolution, However, if the investigator does not believe the Grade IV toxicity presents a significant risk and wishes to continue dosing, the investigator needs to contact _____ of _____ to discuss the patient's toxicity and eligibility for continuation.
DLT: Patients who experience DLT may, at the investigator's discretion, be dose-reduced at 9 µg/kg/d once all of the dosing criteria from the following are met (at least by Day 35 of a cycle, or up to 15 days after the 21-day of the cycle completion) prior to rechallenge:

- Creatinine < 0.4 mg/dl over the baseline value
- Serum albumin > 2.8 mg/dl
- < 50 RBC per HPT on urinalysis
- < 2+ proteinuria on urinalysis
- Blood pressure with systolic ≥ 100 mm Hg or diastolic ≥60 mm Hg
- Orthostatic heart rate change of ≤ 15 (moving from supine to standing)

Any abnormality occurring during or after agent administration should be monitored until return to baseline condition. stabilizes or the reason for persistence is determined.

Response criteria: See the sections entitled Tumor Response Criteria, Measurement of Tumor Burden, and Secondary Endpoints under Protocol 93-04-l 0.

Preliminary Results

The primary source documents (raw data and case report forms) for this study were not submitted in the applications. An interim report containing the baseline entry characteristics and safety information on 40 patients enrolled in this ongoing study were submitted. The pertinent characteristics of for these 40 patients at study entry are summarized in Table 25.
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